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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/849,115 | 05/05/2001 | Emil V. Kozarov | UF-10380 | 9072 |

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| EXAMINER | |
|---|---|
| NICKOL, GARY B | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 10/31/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/849,115 | KOZAROV ET AL. | |
| | Examiner | Art Unit | |
| | Gary B. Nickol Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,11-15 and 21-29* is/are pending in the application.

4a) Of the above claim(s) *21-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

***Response to Amendment***

The Amendment filed August 12, 2003 (Paper No. 18) in response to the Office Action of March 7, 2003 is acknowledged and has been entered.

Claims 5 and 16 are cancelled.

Claims 21-29 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 1-4 and 11-15 are currently under consideration.

**The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.**

**New Rejections**

Claims 1-4 and 11-15 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth a pharmaceutically effective amount of a cysteine protease selected from the group consisting of PrtP, HagA, and a HagArep peptide wherein said protease is derived from the bacterium *Porphyromonas gingivalis*, and therefore the written description is not

commensurate in scope with the claims which encompass "fragments or active sites" derived from said proteases including fragments or active sites derived from any and all organisms.

With regards to any and all organisms including all bacterium, the disclosure fails to include proteases beyond those isolated from the bacterium *Porphyromonas gingivalis*. The specification (page 9, lines 19+) incorporates by reference the teachings of US Patent No. 5,830,710. However, the '710 disclosure only provides a written description of the amino acid sequence by SEQ ID NO: for PrtP and Hag A isolated from *Porphyromonas gingivalis* (see column 3 of US 5830710). Additionally, the teachings of US Patent No. 5,824,791 were incorporated by reference to provide a written description of a HagArep peptide. Such repeating peptide units are disclosed in the '791 patent in columns 3-4 and include HArep1, HArep2, HArep3, and HArep4. However, the written description of such peptides for the incorporation of essential subject matter is solely limited to those peptides derived from the bacterium *Porphyromonas gingivalis* . Thus, claims 1-3 and 11-14 do not meet the written description requirement because the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, which include proteases from **any and all organisms including any and all bacterium**. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Further, the specification does not reasonably convey to one skilled in the art that applicants were in possession of the multitude of various amino acid fragments and or active

sites derived from said proteases which encompasses naturally occurring variant peptide sequences whether they be derived from any and all organisms or isolated from bacterium *Porphyromonas gingivalis*. In the instant case, the written description only sets forth PrtP, HagA, or a HagArep peptide.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only a pharmaceutically effective amount of a cysteine protease selected from the group consisting of PrtP, HagA, and a HagArep peptide wherein said protease is derived from the bacterium *Porphyromonas gingivalis* , but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

**Rejections Maintained:**

Claims 1-4 and 11-15 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record in Paper No. 15, pages 4-8.

Applicants argue (Paper No. 18, page 10) that the use of *in-vitro* tests such as inhibition of VEGF-induced proliferation have been shown to correlate with positive clinical results with, for example, the anti-angioproliferative drug Avastin. Applicants further argue that one of skill in the art at the time the invention was filed would have recognized that inhibition of VEGF-induced proliferation of endothelia cells is a reasonably correlating example of angiogenesis. Applicants further argue that where a particular model is recognized in the art as reasonably correlating to a specific condition, it should be accepted as correlating by the Examiner. Applicants further argue that the instant invention was tested with an in-vitro VEGF-induced proliferation inhibition assay similar to the in vitro tests performed for Avastin and in Schlaeppi *et al.*

These arguments have been considered carefully but are not found persuasive. While it may be reasonable to conclude that the instant invention has some effect on the detachment of endothelial cells in culture (page 19, line 10), the examples in the specification do not appear to teach that the instant invention was tested using "VEGF-induced" proliferation. For example, working examples 1, 2, 7, and 11 as attested to by applicant (Paper No. 18, page 11) do not appear to teach that VEGF was included in the experiments to induce growth. Thus, it cannot be

ascertained that applicants in-vitro model reasonably correlates to the experiments taught in the art. Also, the journal articles which applicants have referred to (i.e. Presta *et al.*, and Schlaeppi *et al.*) could not be found attached to applicant's response. However, even in the absence of such articles, evidence of enablement for a particular biological molecule known in the art (i.e. Avastin) does not extrapolate or reasonably predict the enablement of a completely distinct biological molecule because it has not been demonstrated that the currently claimed molecules have any in-vivo effects which correlate to their in-vitro activity. And, as mentioned previously, it is well known in the art that "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease.

Applicants further argue (Paper No. 18, page 11-12) that treating cancer does not require complete cures and that the Office appears to require detailed clinical trials on human populations in order to satisfy the enablement requirement. This argument has been considered but is not found persuasive. While it is true that treating cancer does not require complete cures, there is no evidence to suggest that the claimed method would elicit any cures in a patient. Further, the issue of detailed clinical trials is not limited to human trials as suggested by applicant. This was previously addressed because the claims included a method for preventing a cancer which applicants are not enabled for as set forth in the previous Office Action.

Thus, applicant's arguments have not been found persuasive and the rejection is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
October 30, 2003